# Pharmacokinetic Modeling of PFOA and PFOS

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# Background

- Estimating exposure of humans to PFOA and PFOS from measured concentrations in serum has been complicated by
    - lack of pharmacokinetic data in humans
    - evidence from animal studies that the kinetic behavior is complex

- In this study, a physiologically based pharmacokinetic (PBPK) model of PFOA and PFOS kinetics in the monkey and rat was scaled to the human and validated against data from a population exposed to high concentrations of PFOA in drinking water

- This model can be used for exposure reconstruction and cross-species dosimetry in support of risk assessments

# Absorption, Distribution, Metabolism

## Absorption
- Good intestinal absorption and enterohepatic circulation
- Poor dermal absorption

## Distribution
- > 97% bound in plasma (largely to albumin & β-lipoprotein)

- Rapid approach to steady state at high concentrations
  - inconsistent with long terminal half-life

## Metabolism
- No significant metabolism

# Clearance

## Excretion

- Urinary excretion
  - Organic Anion Transporter (OAT)
    - active secretion
  - Organic Anion Transporter protein (OATp)
    - active resorption from renal tubule

- Biliary/fecal excretion
  - Enterohepatic recirculation
  - OAT/OATp mediated transport

- Inter-species and sex differences in elimination half-life (PFOA):
  - 3 hours in female rats vs. 5 days in male rats
  - 20 days in monkeys vs. 4 years in humans

# Dose-Dependent Distribution

Can estimate apparent volume of distribution at end of study using this simple equation

$$Vd_{SS} = (\text{dose rate})/(k_{elim}*C_{blood})$$

where $k_{elim} = 0.693/t_{1/2}$

Dose-dependence of volume of distribution would indicate change in kinetic processes as dose increases and failure of one-compartment model

# PFOA Kinetic Parameters Change with Dose

| Species | Daily dose mg/kg/day | $V_{dss}$ (liters) | Reference |
|---------|----------------------|--------------------|-----------|
| Male rat -28 days | 0.06<br>0.64<br>1.94 | 0.1<br>0.2<br>0.3 | Palazzolo (1993) |
| Male rat -28 days | 3<br>10<br>30 | 0.7<br>1.4<br>6.4 | Hankijarvi et al. (1987) |
| Male monkey 6 months | 3<br>10 | 1.26<br>3.73 | Butenhoff et al. (2002) |
| Male monkey 90 day | 3<br>10 | 1.81<br>5.21 | Griffith and Long (2002) |

## Suggests 1-compartment model inadequate

# Schematic for a simple renal resorption pharmacokinetic model for PFOA and PFOS in the monkey
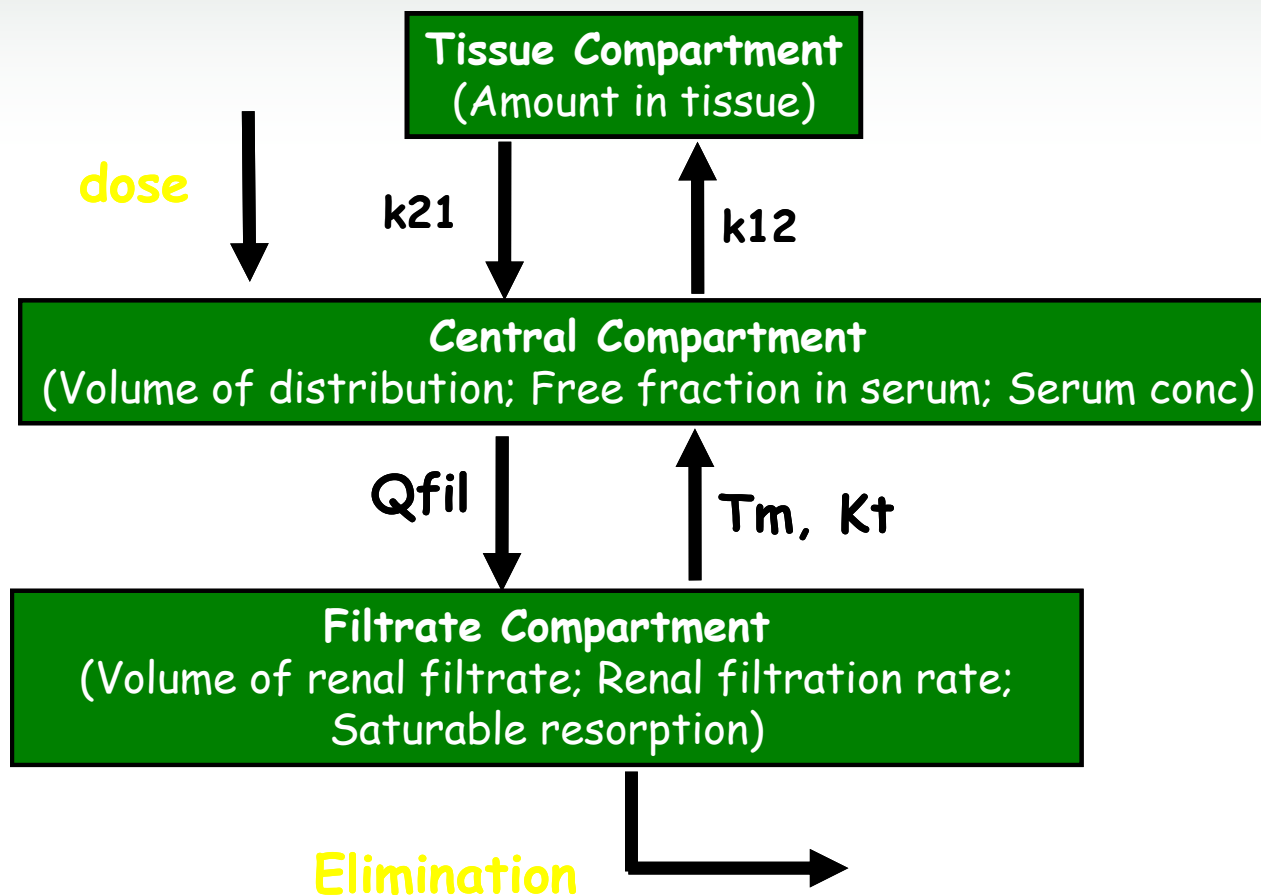
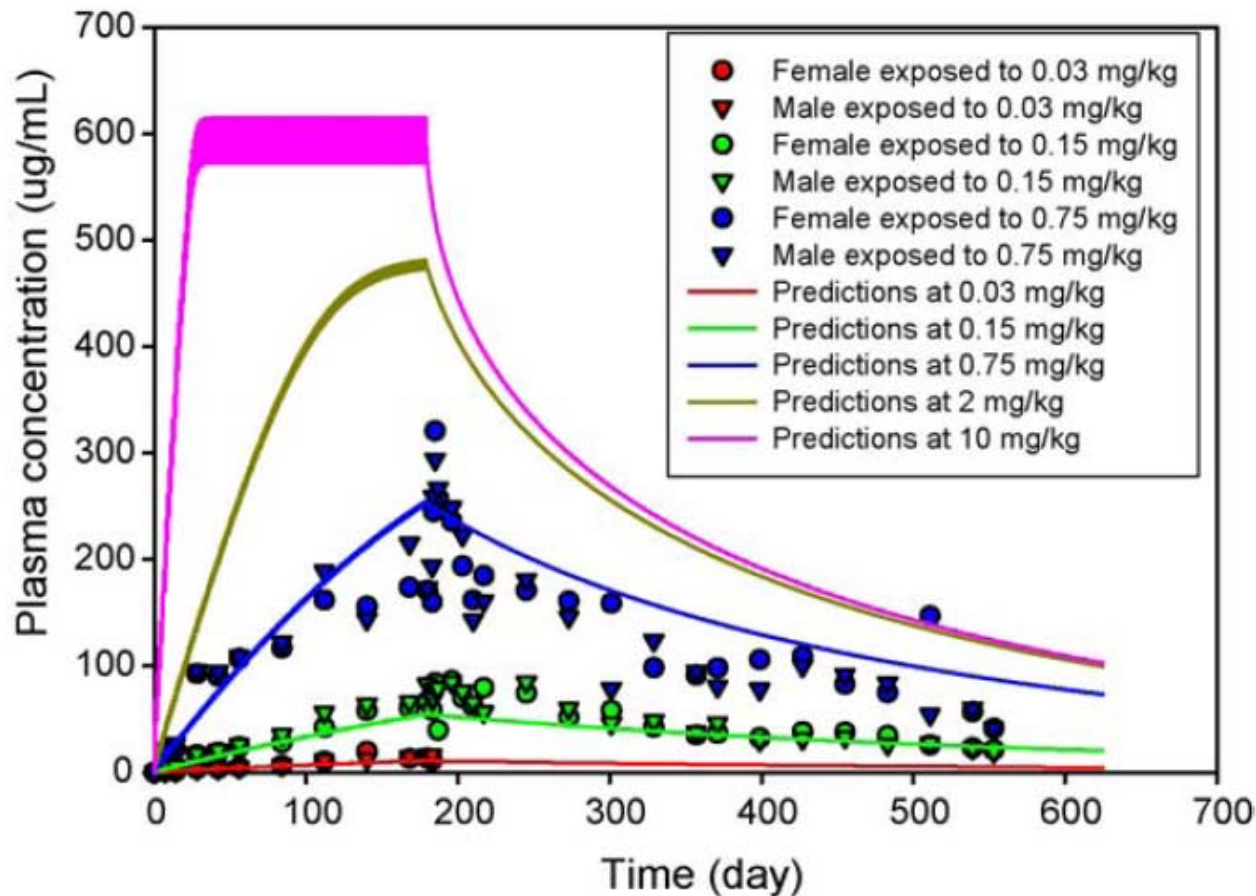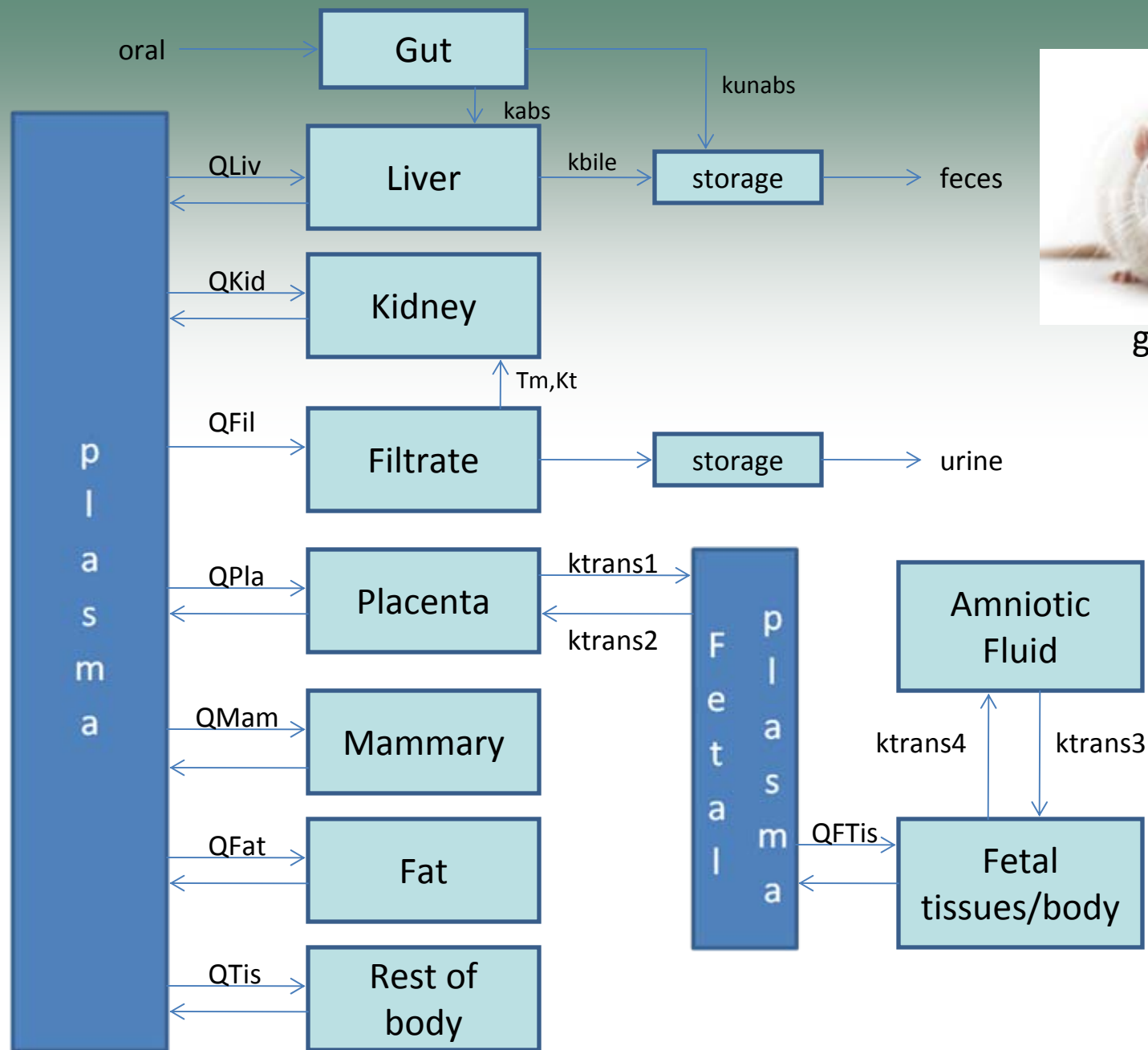# Time course of PFOA in plasma and urine of cynomolgus monkeys dosed daily with 20 mg/kg PFOA

Andersen et al. (2006)
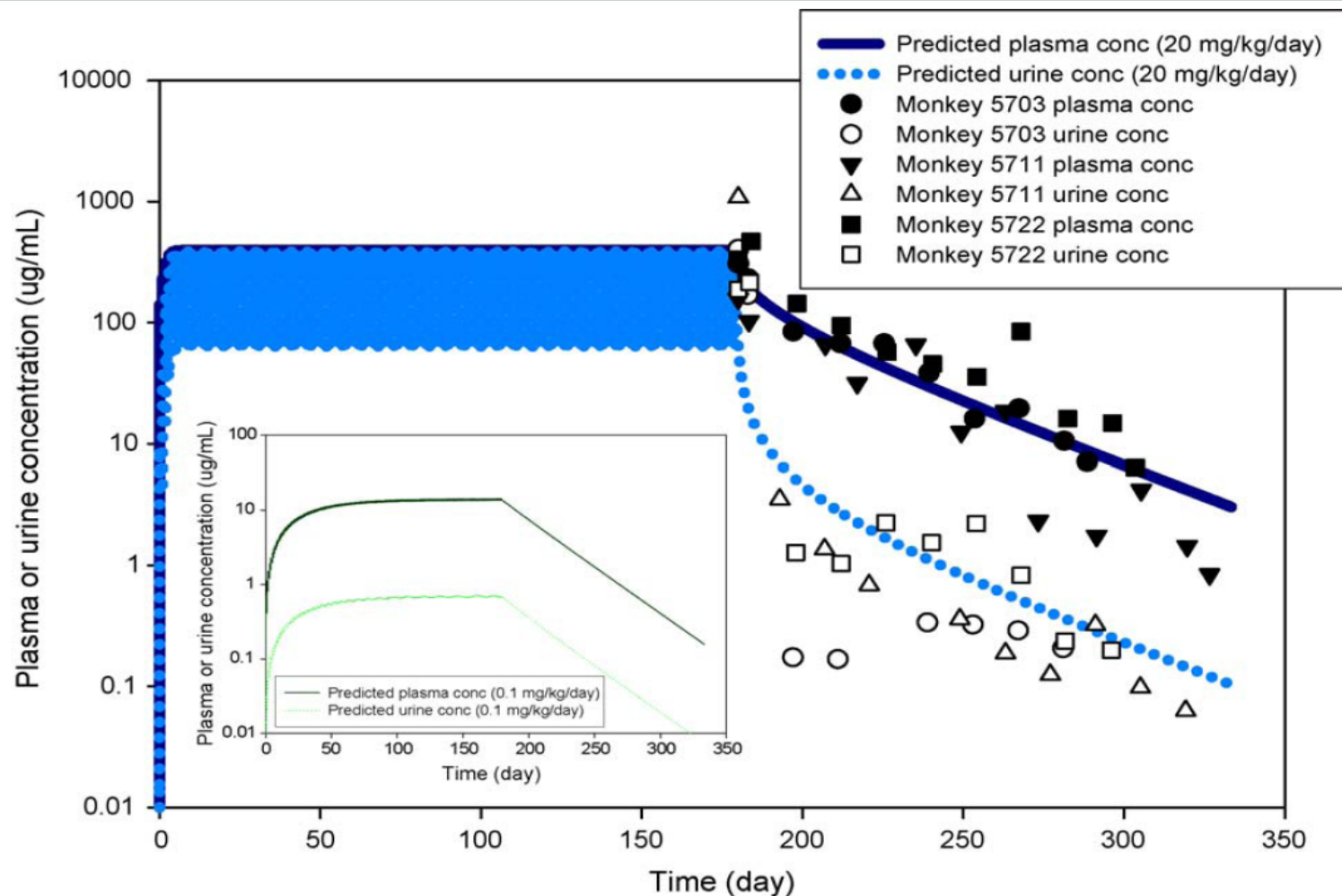
# Modeling Serum after Cessation of Daily Dosing with PFOS

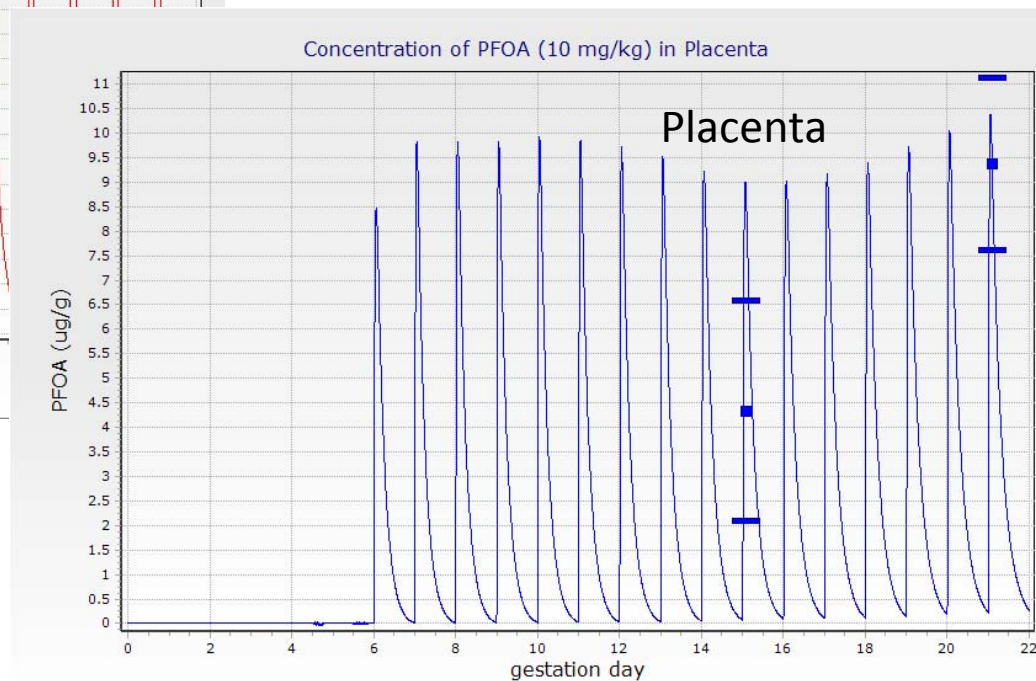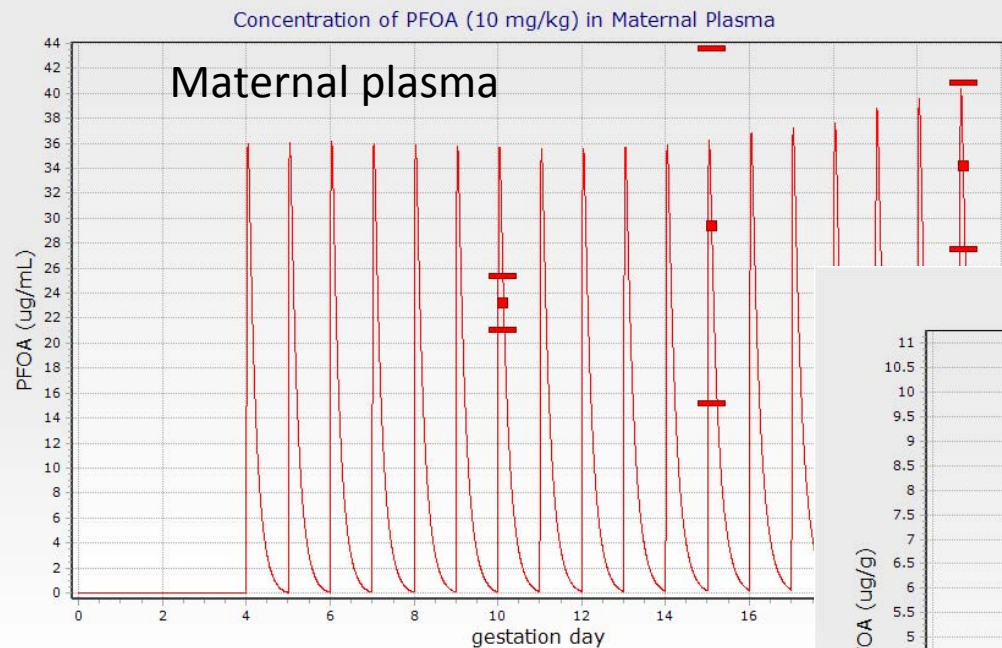Andersen et al. (2006)

# Progress on PBPK Models for PFOA and PFOS

• The renal resorption pharmacokinetic model originally applied to monkeys and humans has now been extended to mice by scientists at EPA NHEERL, including gestation and lactation exposure

• At The Hamner, a PBPK model of PFOA and PFOS in the monkey and rat has been developed.

  • The rat model has been extended to describe gestation and lactation exposures

  • The monkey model has been scaled to the human and validated against data from populations exposed to high concentrations of PFOA in drinking water

  • The human model can be used for exposure reconstruction and cross-species dosimetry in support of risk assessments
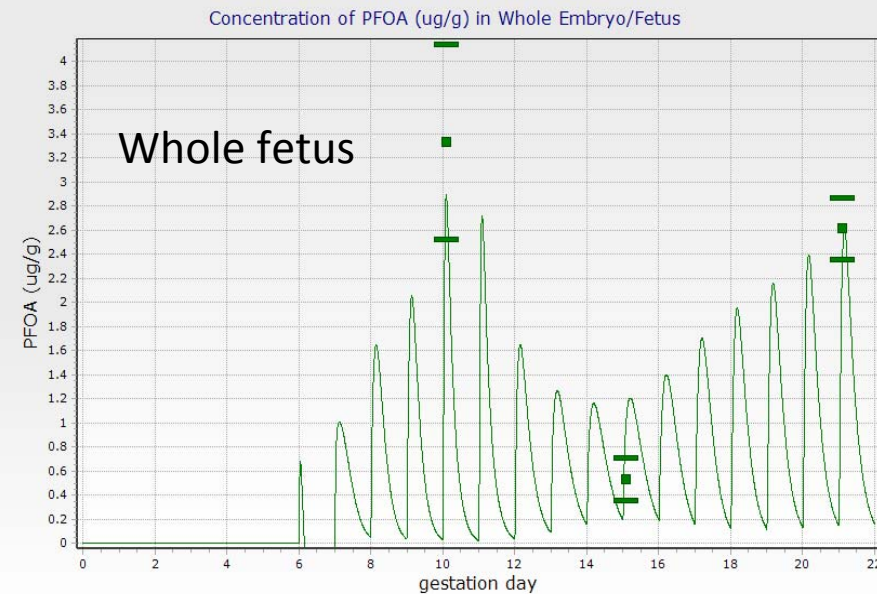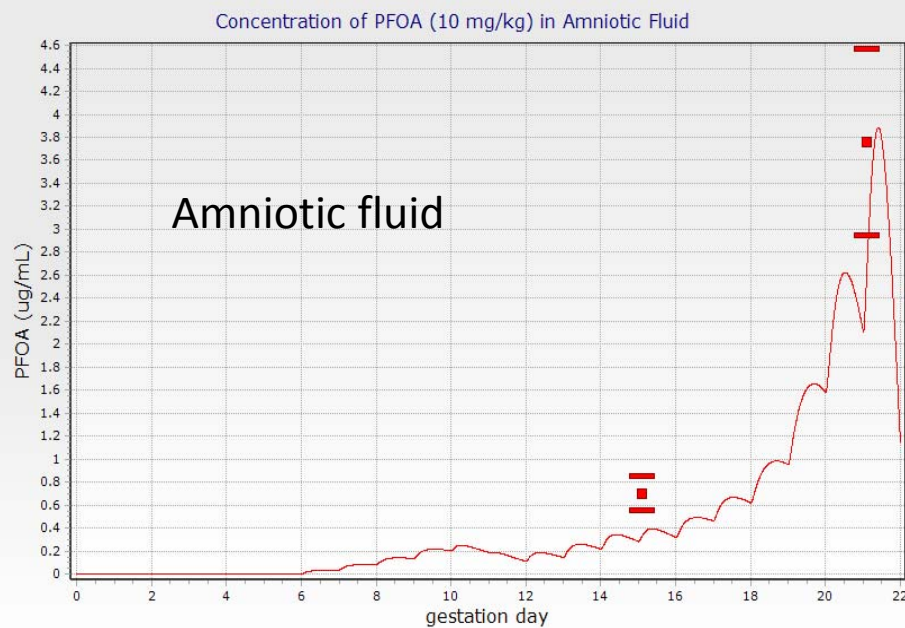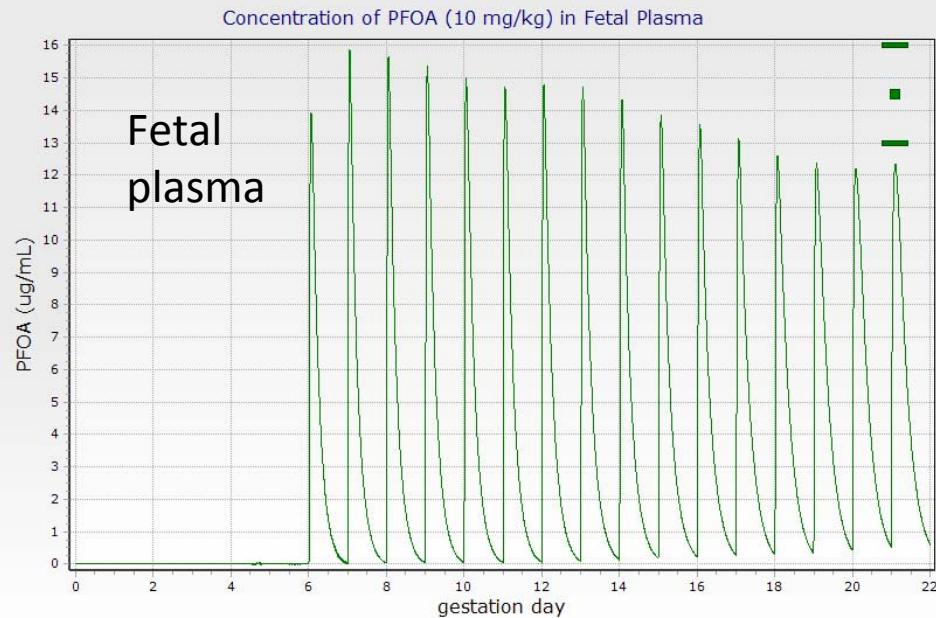
gestation

# PFOA

Experimental data from Hinderliter, et al.[*]



Concentration of PFOA (10 mg/kg) in Maternal Plasma — Maternal plasma



Concentration of PFOA (10 mg/kg) in Placenta — Placenta

[*] Hinderliter, et al. 2005, Toxicology, 211, 139.

# PFOA

**Concentration of PFOA (10 mg/kg) in Fetal Plasma**

Fetal plasma

10 mg/kg PFOA to dam (GD4-GD21)

**Concentration of PFOA (10 mg/kg) in Amniotic Fluid**

Amniotic fluid

**Concentration of PFOA (ug/g) in Whole Embryo/Fetus**

Whole fetus

# PFOS

**Maternal plasma**

Model: 3.53

Mean: 1.72

0.1 mg/kg PFOS to dam (GD0 through GD19)

Experimental data from Chang, et al.[7]

**Maternal brain**

Model: 0.214

Mean: 0.151

**Maternal liver**

Model: 15.7

Mean: 8.4
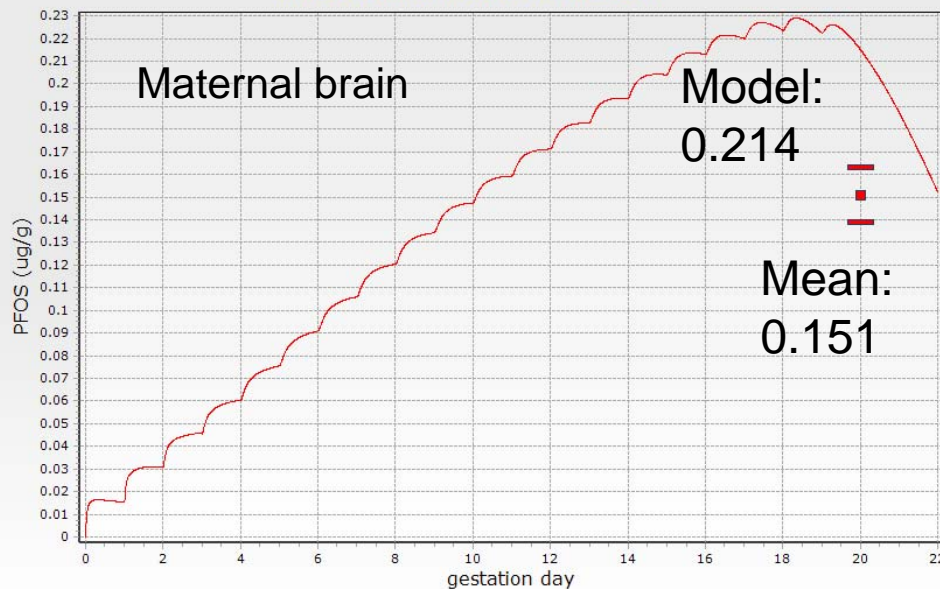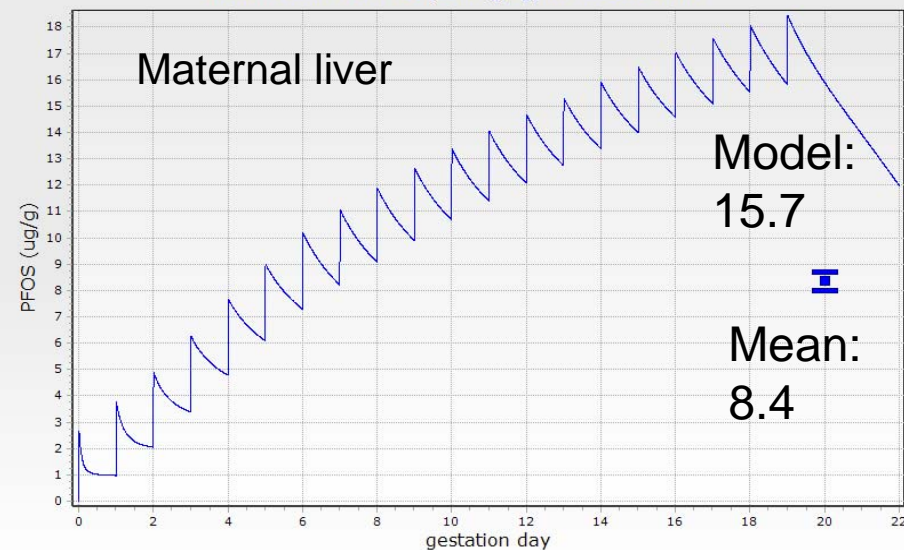
7. Chang, et al. *2009*, Reprod. Tox.,27, 287-299.

# PFOS

**Concentration of PFOS (0.1 mg/kg) in Fetal Liver**

Fetal liver

Mean: 3.2

Model: 2.5
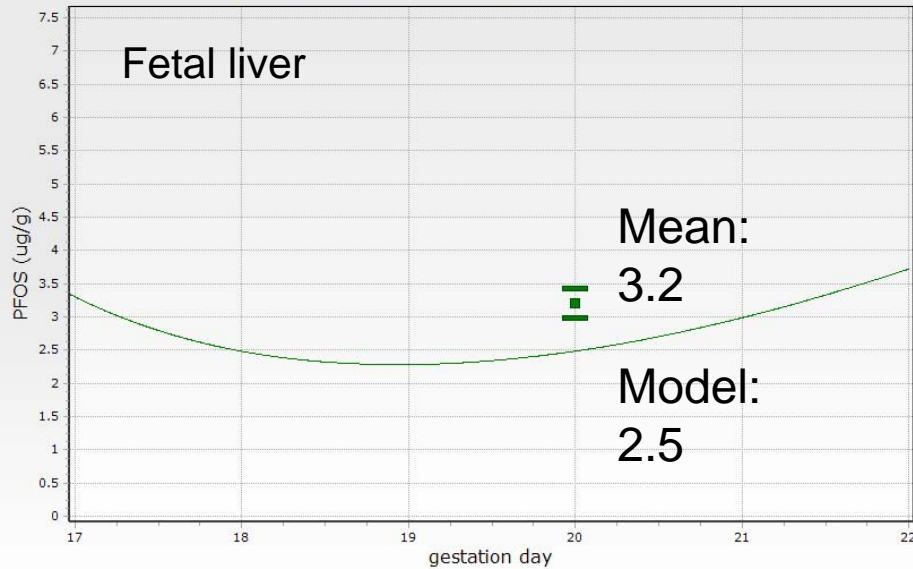
Fetal tissue concentrations for 0.1 mg/kg PFOS to dam (GD0-GD19)

**Concentration of PFOS in Fetal Brain (0.1 mg/kg)**

Fetal brain

Model: 1.7

Mean: 1.2

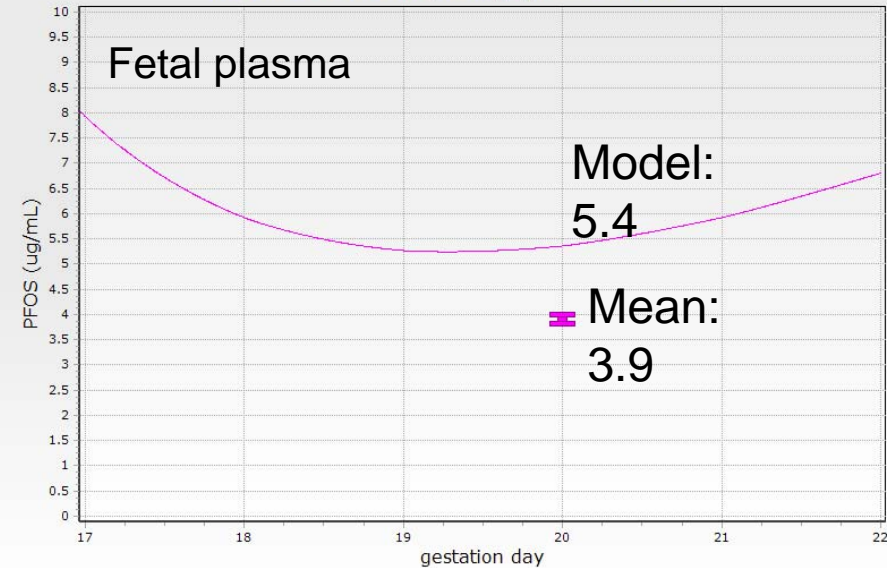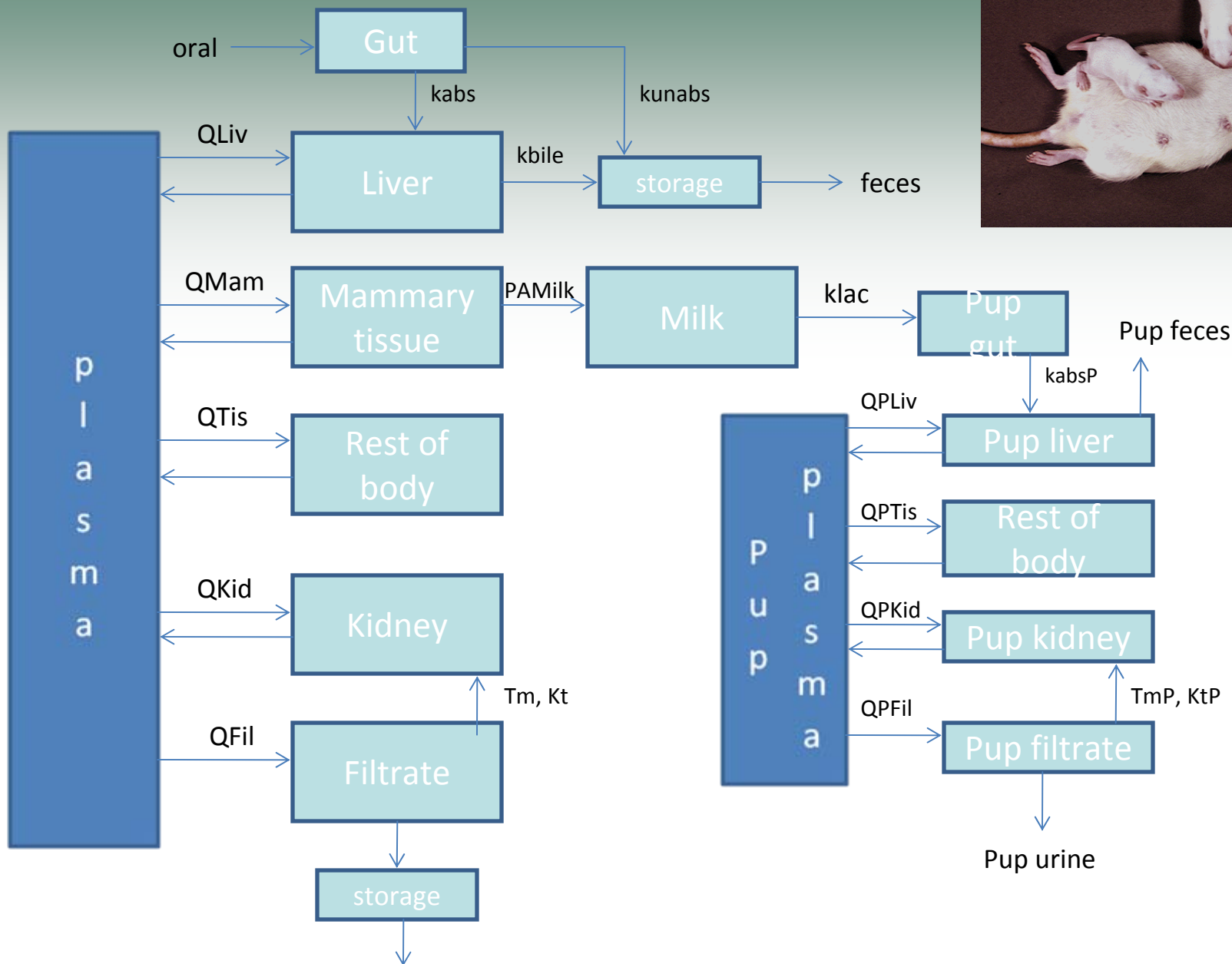**Concentration of PFOS (0.1 mg/kg) in Fetal Plasma**

Fetal plasma

Model: 5.4

Mean: 3.9
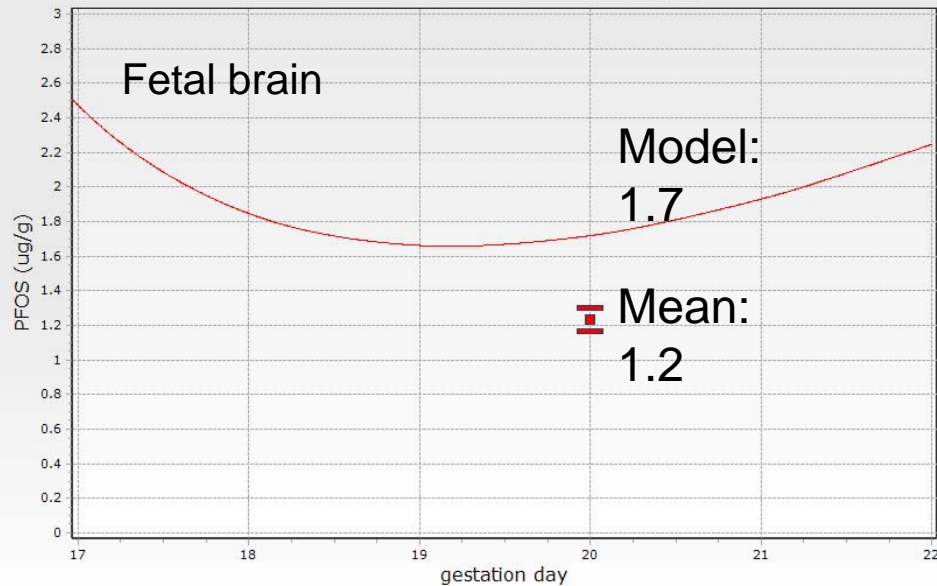
lactation

Concentration of PFOA (10 mg/kg) in Maternal Plasma

Maternal plasma
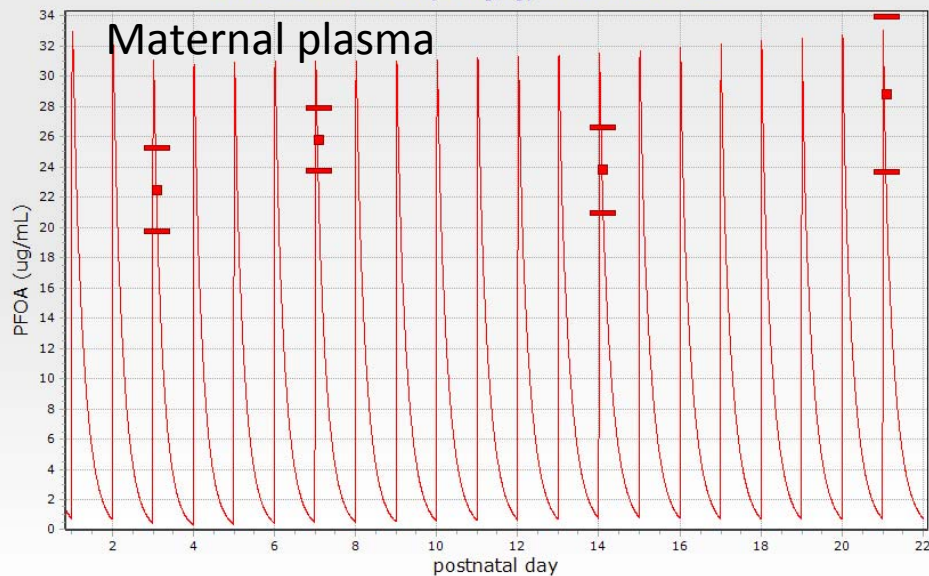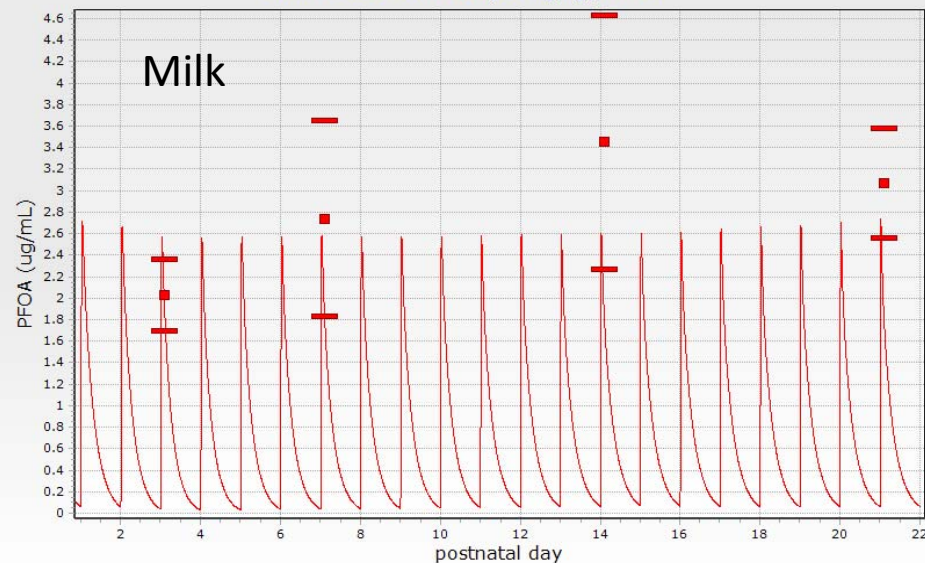

Concentration of PFOA (10 mg/kg) in Milk

Milk


Concentration of PFOA (10 mg/kg) in Pup Plasma

Pup plasma
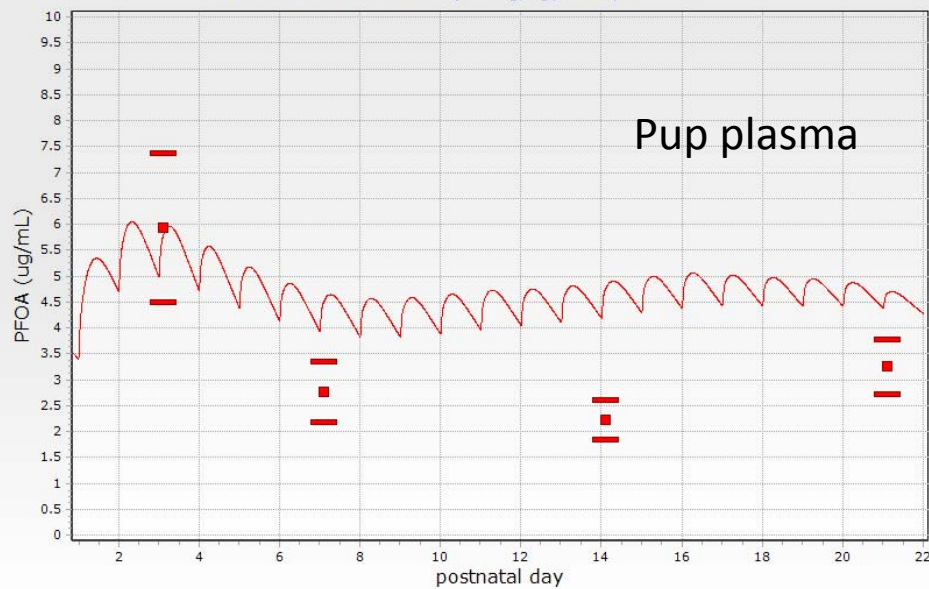
10 mg/kg PFOA to dam (GD4-PND21)

Experimental data from Hinderliter, et al.

# PFOA

Oral dose

Gut

QGut

Liver

QLiv

Fat

QFat

IV

Skin

QSkn

Rest of body

QR

Kidney

QKid

Tm,Kt

Filtrate

QFil

storage
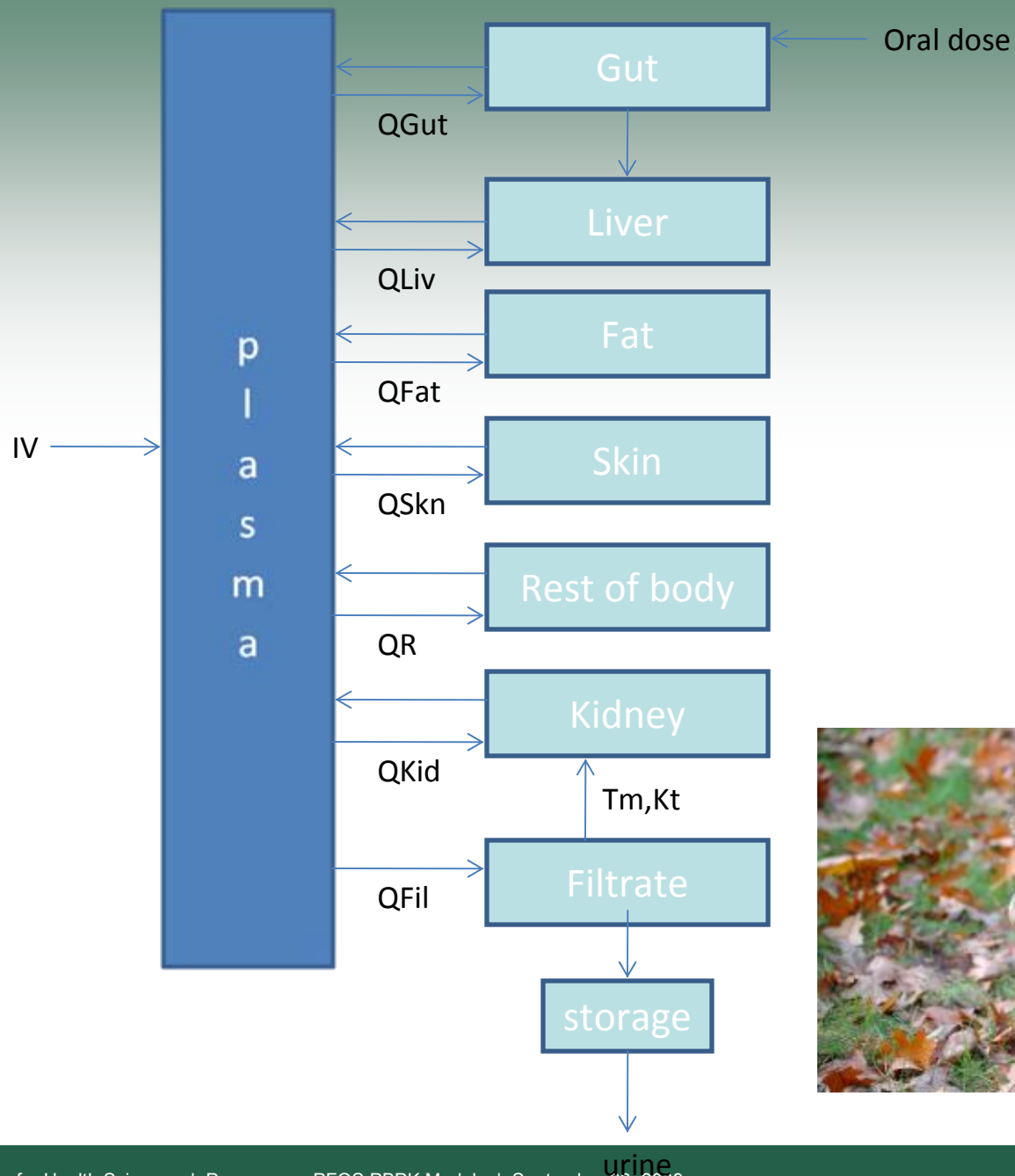
urine

plasma

PFOA in monkey plasma (10 mg/kg)


PFOA in urine (10 mg/kg)
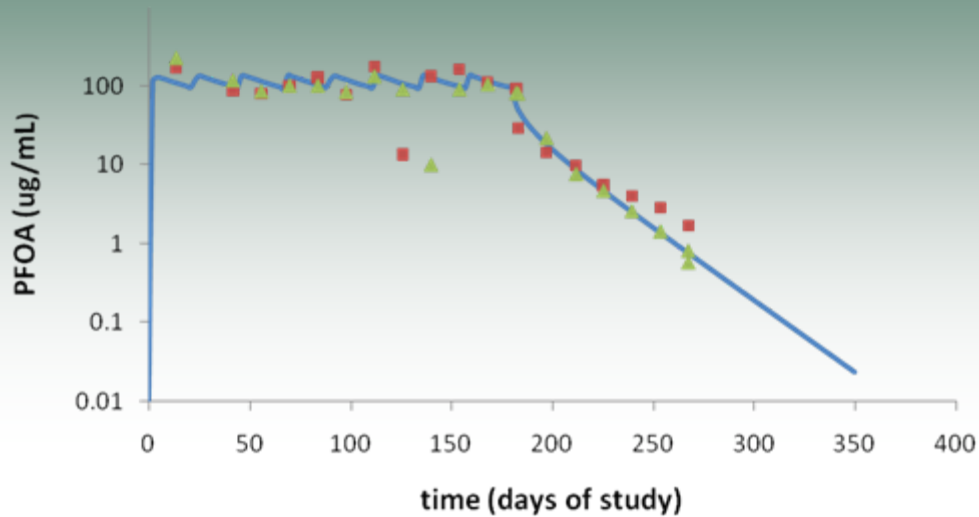
Oral dose of 10 mg/kg PFOA to male monkeys for 6 months

Experimental data from Butenhoff, et al.[5]
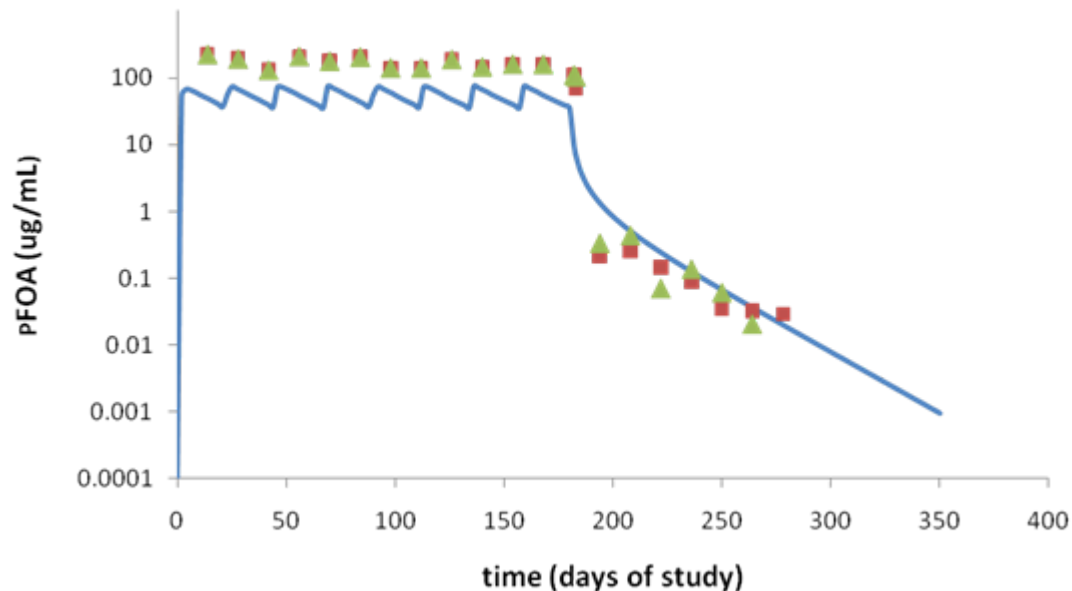
5. Butenhoff, et al. 2004, Tox. Sci., 82, 394.

PFOS concentration in plasma
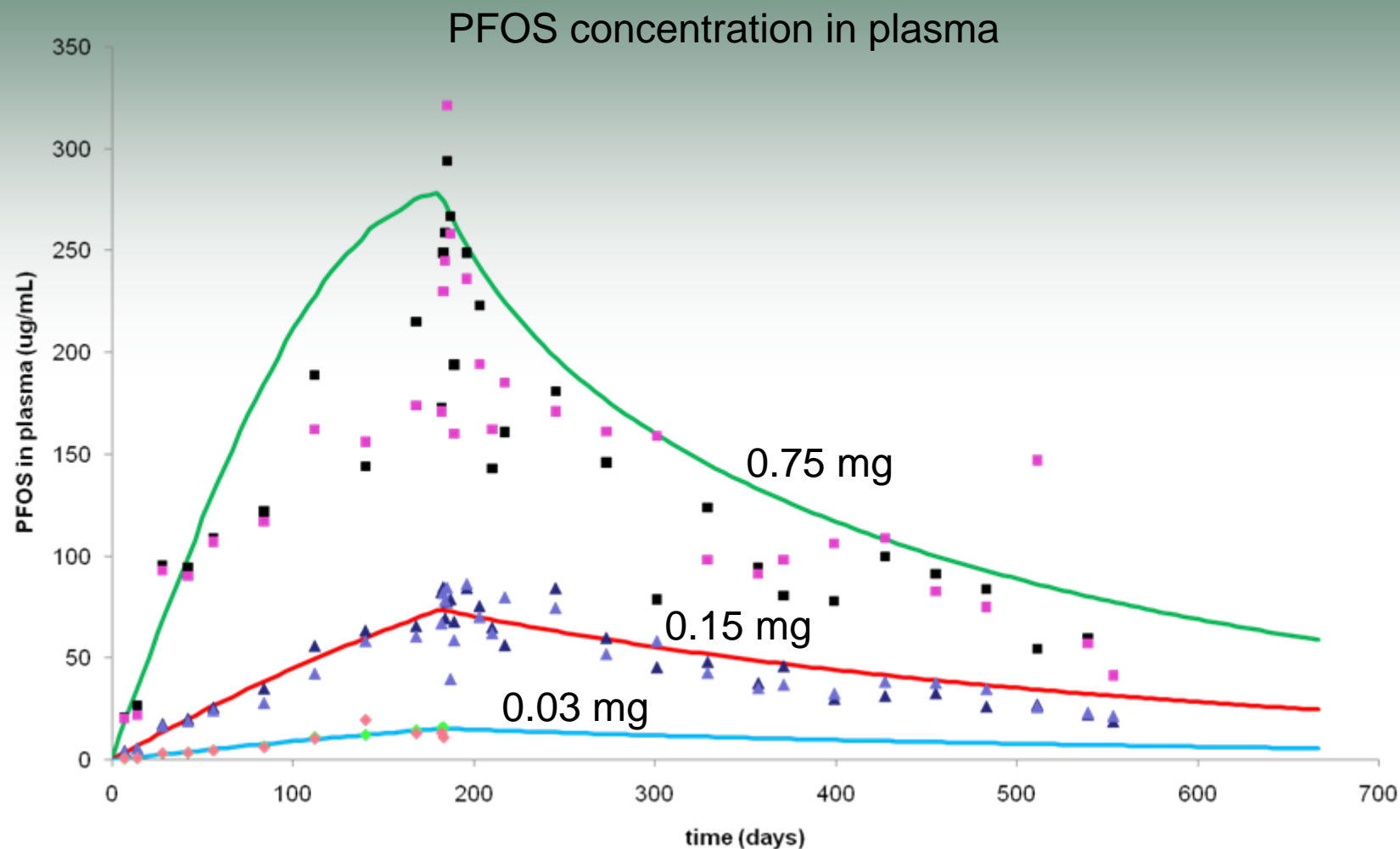
Oral doses for 6 months in male and female monkeys

Experimental data from Seacat, et al[9]
9. Seacat, A.M., et al, 2002, Tox. Sci, 68, p. 249-264.

Human
PBPK Model
for PFOA
and PFOS

(Developed
under EPA
STAR Grant)

Gut — Oral dose, Drinking H2O
QGut

Liver
QLiv

Fat
QFat

Skin — Dermal
QSk

Rest of body
QR

Kidney
QKid
Tm,Kt

Filtrate
QFil

storage

inhalation

# Human PFOA Model Parameters

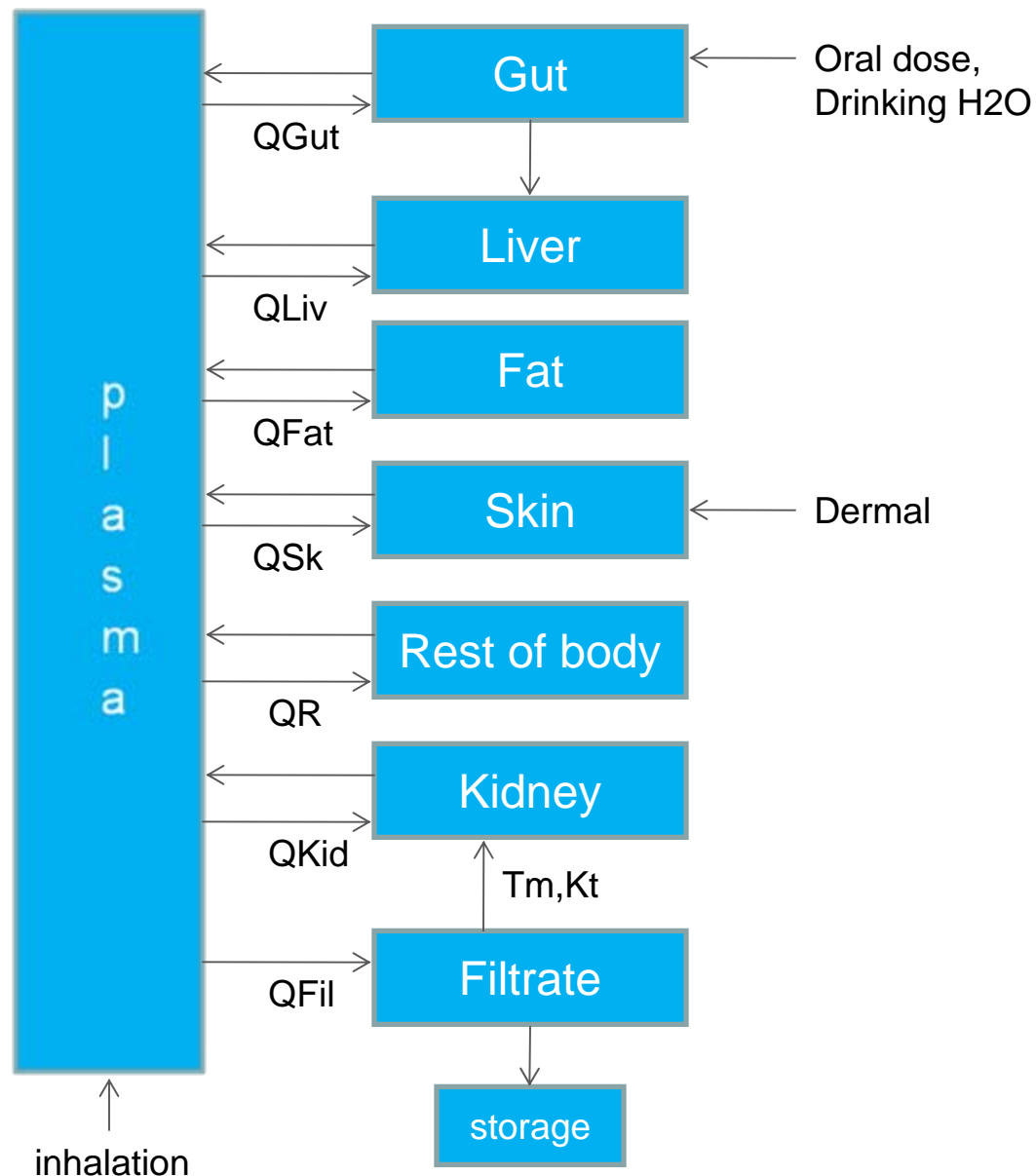| Parameters | Values | Sources |
|---|---|---|
| Body Weight (BW) | 70 kg | EPA Default |
| Cardiac output (QCC) | 12.5 L/h/kg$^{0.75}$ | Brown et al., 1997 |
| Volume of renal filtrate (Vfil) | 0.01 L | Assumed (insensitive) |
| Renal filtration rate (Qfilc) | 8.75% of QCC | Renal plasma flow |
| Volume of distribution (Vdc) | 0.14 L/kg | Estimated (monkey data) |
| Transport maximum (Tmc) | 32.4 mg/kg/h (vs. 5 for monkey) | Adjusted to produce reported half-life of 3.8 years |
| Transport affinity (Kt) | 0.055 mg/L | Estimated (monkey data) |
| Transfer rate constant (K12) | 3.3 /h | Estimated (monkey data) |
| Transfer rate constant (K21) | 0.1 /h | Estimated (monkey data) |
| Free fraction in plasma (Free) | 0.02 | Estimated (monkey data) |

# PFOA Drinking Water Exposure
# Little Hocking, OH

| Parameter | Value | Source |
|---|---|---|
| PFOA in water | Mean: 3.55 ppb (Range: 1.5 – 7.2) | Emmett et al., 2006 |
| Intake | Mean: 13 mL/kg/day (Range: 1 - 95) | EPA-822-R-00-008 |
|  |  |  |
| PFOA in serum drinking water source: tap water only (N = 291) | Mean: 448 ng/mL Median: 374 ng/mL Interquartile range: 221-576 ng/mL | Emmett et al., 2006 |

# Predicted time course of PFOA in an individual exposed daily to 3.55 ppb PFOA in drinking water
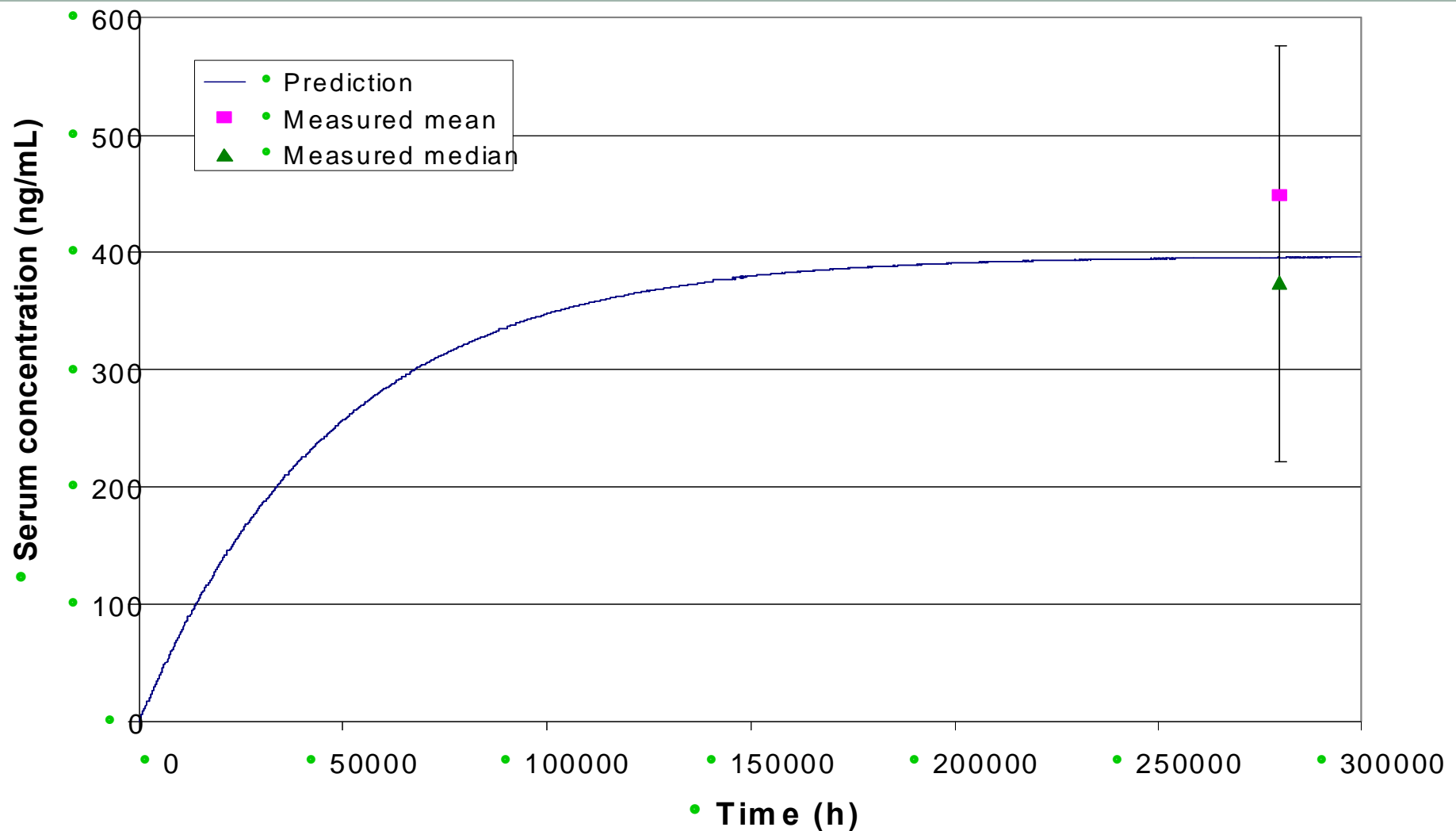
Filtration systems installed in public water systems in Little Hocking. These have decreased the water concentration of PFOA to ~1/2 of what it was in 2006. C8 Health Project measured PFOA serum concentration in 2008, which have decreased to ~1/2 of what they were in 2006. Squares are measured plasma concentrations.



Mean in 2006: 448 µg/L

Mean in 2008: 227 µg/L
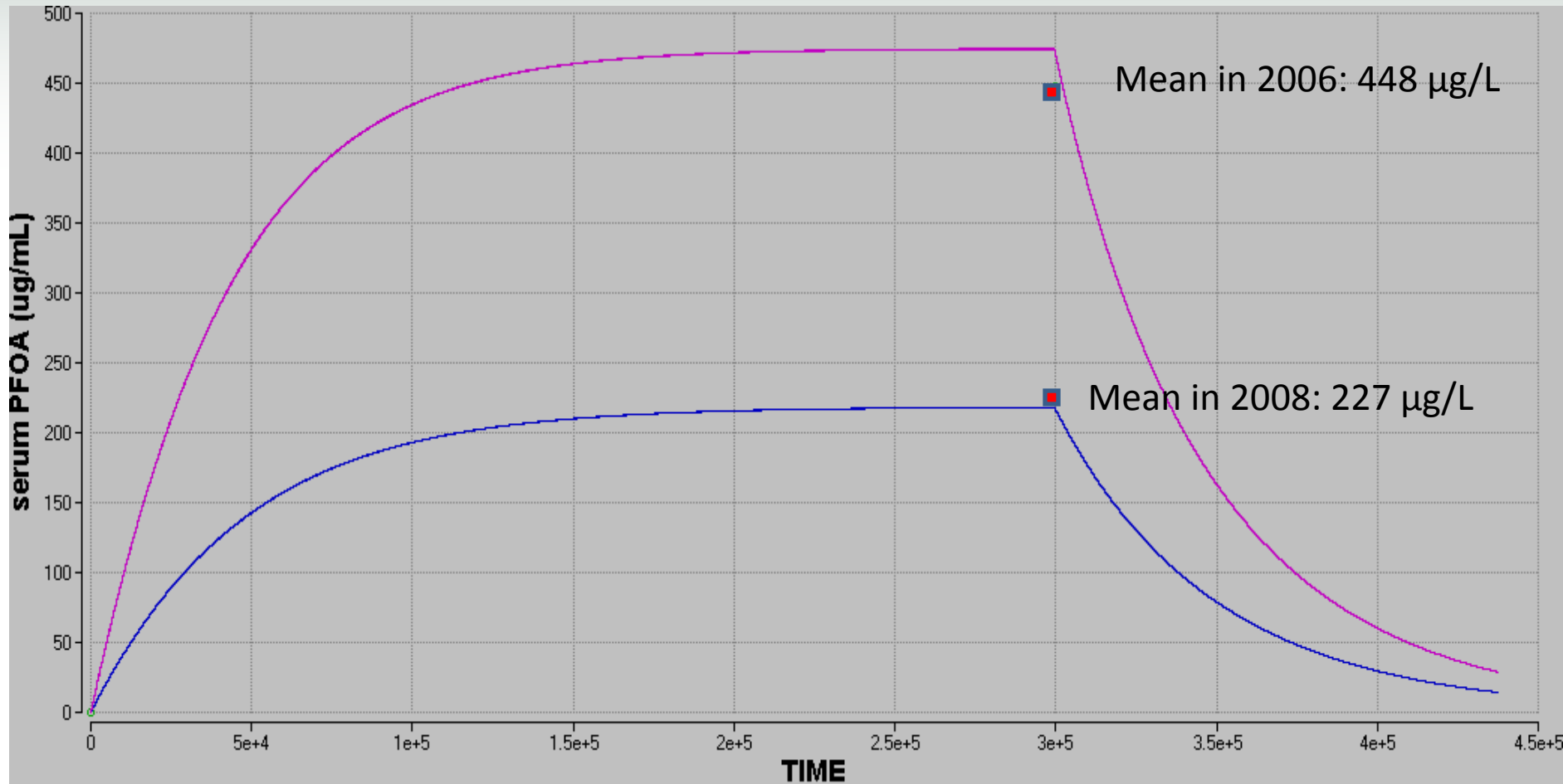
# Human PFOA Model—Arnsberg, Germany Population

Study conducted in Arnsberg, Germany measured a concentration of 0.519 µg/L PFOS in drinking water.[8]

The human PBPK model was used to predict the serum PFOA concentrations and compared with the measured concentrations using the measured drinking water concentration.

Measured mean and SD for serum PFOA was 28.8 ± 12.9 µg/L.

Assumed drinking water rate of 13 mL/kg/day and a half-life of 3.8 years from occupational data.[9]

Duration of exposure was unknown but appeared to be on the order of a few years.

[8]Holzer, et al., *2008*, EHP, *116*, 651-657.
[9]Olsen, et al., *2007*, EHP, *115*, 1298-1305.

Serum PFOA model predictions after different exposure periods compared to measured serum PFOA in Arnsberg population (open circles)
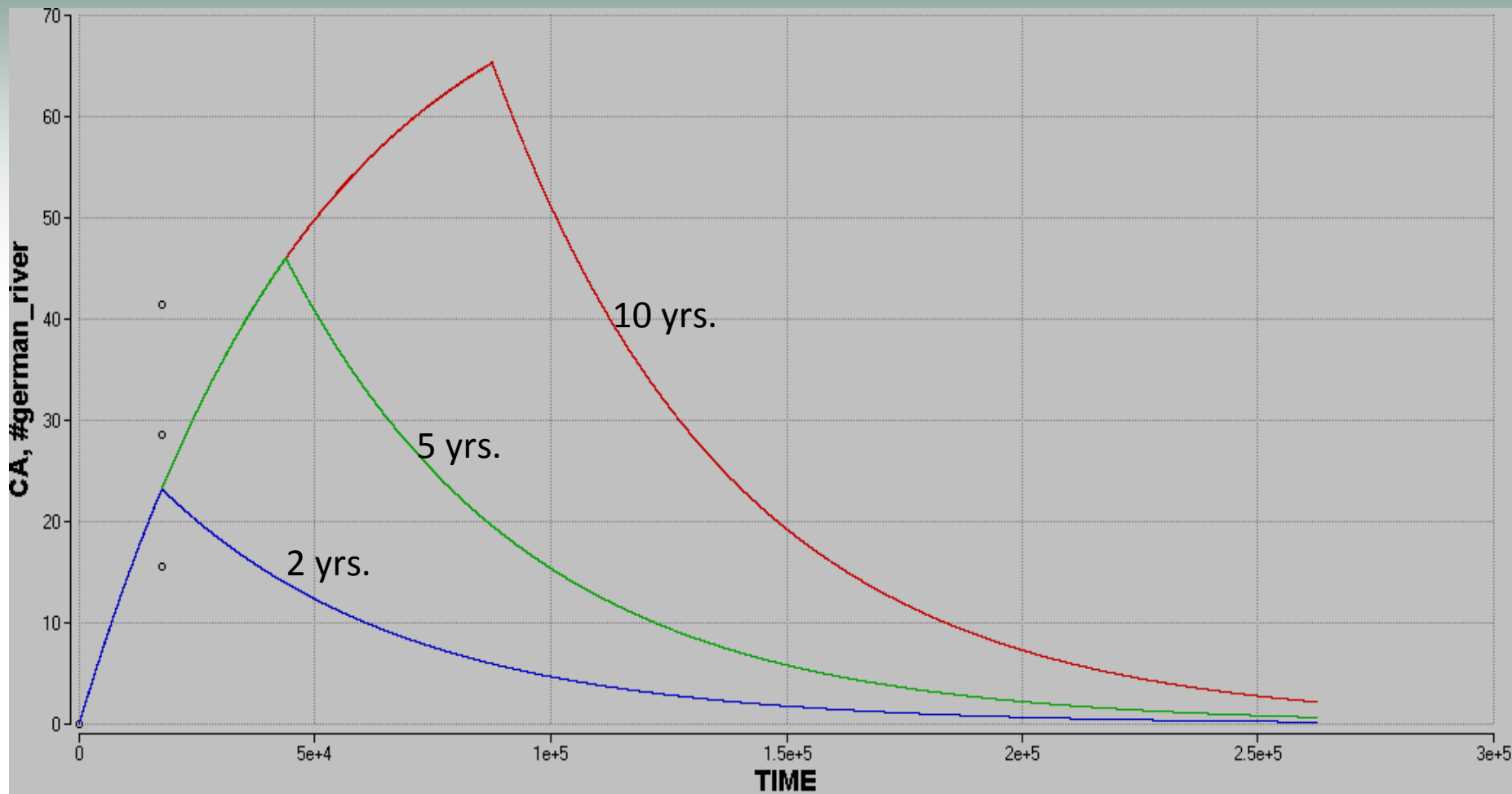


It is not known how long the population was exposed; however, using the measured drinking water concentration of 0.519 ppb, ~1.5 to 4 years was enough time to reach the measured plasma concentration.

# Why a biologically based model?

- For human environmental exposures the predictions of the biologically based model are similar to those obtained using a one-compartment model with a half-life of 3.8 years and a volume of distribution of 0.23*BW.

- However, the physiological structure allows prediction of potentially nonlinear kinetics at higher (occupational) exposures

- In addition, the fact that the model parameters possess physiological meaning makes it possible to evaluate the potential for predisposing factors in sensitive individuals

# Parameter Sensitivity of PFOA Model and Implications for Susceptibility
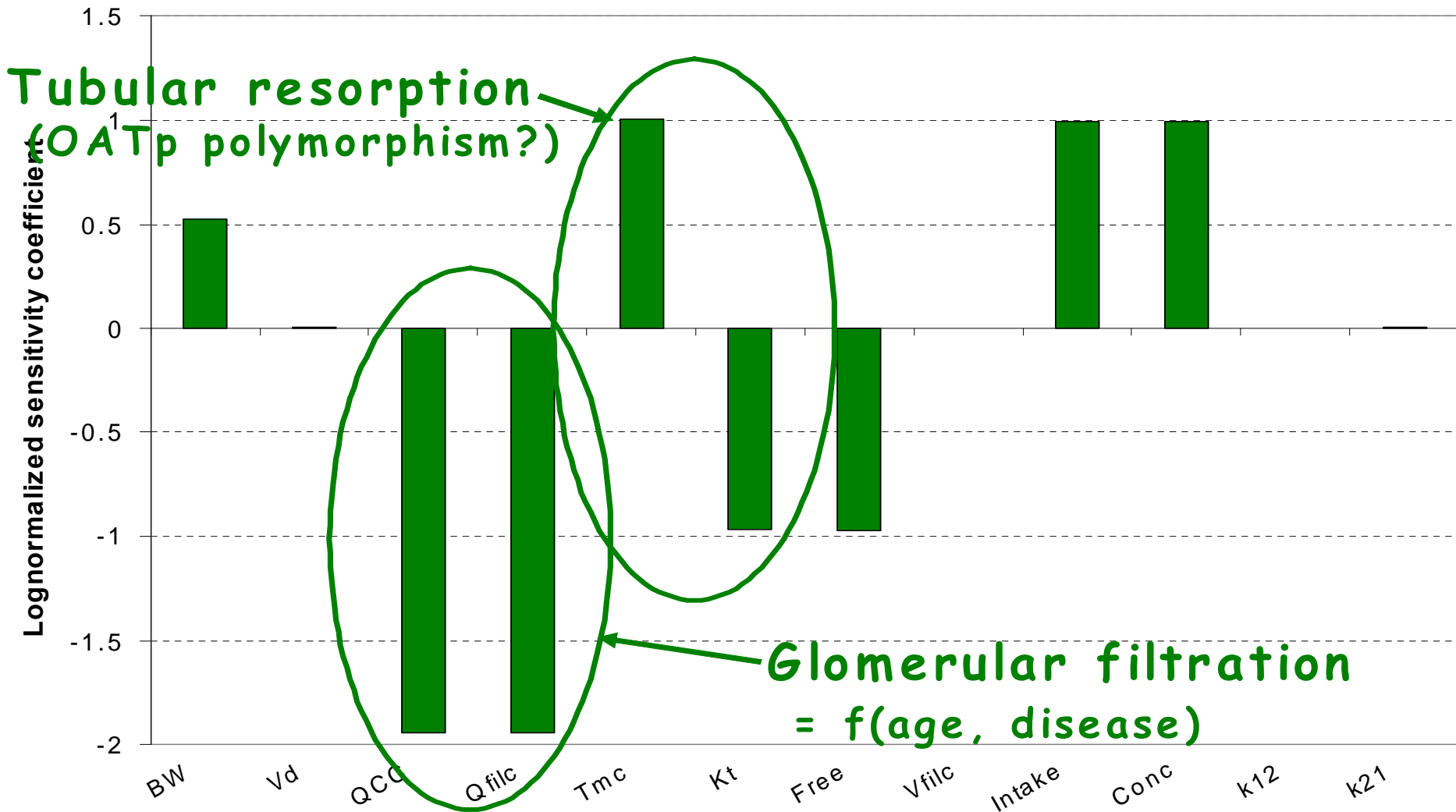
# SUMMARY:

- The observed kinetics of PFOA and PFOS are inconsistent with a one-compartment description

- A description than includes saturable renal resorption is consistent with the kinetic data in the monkey and rodent as well as with what is known about renal transporters for organic acids

- A biologically motivated model of PFOA in the human has been developed that can be used in estimating exposures associated with measured serum levels

# SUMMARY:

- The model predicts that environmental exposures to PFOA (in ng/kg/day) can be roughly estimated as 0.12 times the serum concentration (in ng/mL)
  - E.g., current "background" PFOA plasma concentrations of ~ 5 ng/mL imply an exposure of ~ 0.6 ng/kg/day

- The ratio predicted for PFOS is 0.10 ng/kg/day per ng/ml in serum

# Example of a PK Risk Assessment for PFOA

- **Serum Concentrations Associated with Toxicity Endpoints in Animals:**

| Endpoint | $BMDL_{IC}$* (ug/ml) |
|---|---|
| 6-month monkey liver weight | 23 |
| Rat post-natal effects | 29 |
| Rat Leydig cell tumors | 125 |

* Lower bound benchmark plasma concentration (from Butenhoff et al., 2004)

- **Uncertainty factor: 30**
  - 3 for animal-to-human pharmacodynamics
  - 10 for human variability

- **Resulting RfD: 0.09 μg/kg/day**
  - Exposure predicted to produce a blood concentration of 0.77ug/ml (23/30)

# Example of a PK Risk Assessment for PFOS

- Serum Concentrations Associated with Toxicity Endpoints in Animals:

| Endpoint | $BMDL_{IC}$* (ug/ml) |
|---|---|
| • 6-month monkey clinical endpoints | 35 |

\* Lower bound benchmark plasma concentration (from Butenhoff et al., 2004)

- Uncertainty factor: 30
  - 3 for animal-to-human pharmacodynamics
  - 10 for human variability

- Resulting RfD: 0.12 $\mu$g/kg/day
  - Exposure predicted to produce a blood concentration of 1.17ug/ml (35/30)

# EPA STAR Grant: Future Directions

Lifeline Group will integrate our PBPK model with their exposure model.

The combined exposure/PBPK model will be exercised to establish the relationship between potential exposure sources and observed serum levels in human populations.

# Acknowledgements

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